Docket No.: BULK 3.0-018

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of: Manne S. REDDY et al.	:	
Application No.: 10/601,844	:	Group Art Unit: 1624
Filed: June 23, 2004	:	Examiner: Ward, Paul V.
For: AMORPHOUS LEVOCETIRIZINE DIHYDROCHLORIDE	:	

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

REPLY BRIEF

Sir:

This paper is submitted in response to the Examiner's Answer mailed on May 3, 2010, in the above-identified application. Submission of a reply brief in this case is due by July 6, 2010. Accordingly, this paper is being timely filed.

Appellants respectfully request that the following remarks be considered.

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1. Status of the Claims

Claims 1-18 stand finally rejected, and are the subject of this appeal. Claim 23 was cancelled, and claims 19-22 and 24-37 were withdrawn from consideration.

2. Grounds of Rejection to be Reviewed on Appeal

A. Whether claims 2 and 10 are indefinite under 35 U.S.C. § 112, second paragraph.

B. Whether claims 1-16 are anticipated under 35 U.S.C. § 102 by any of Tang et al., *J. China Pharm. Univ.*, 2002 ("Tang"), Pflum et al., *Organic Process Research and Development*, 2002 ("Pflum") and Van de Venne et al., U.S. Patent No. 6,489,329 ("Van de Venne").

C. Whether claims 17 and 18 are obvious under 35 U.S.C. § 103 over Van de Venne.

3. Argument

Appellants maintain that each of the Examiner's rejections is improper and should be reversed.

A. The Examiner maintains that claims 2 and 10 are indefinite for the use of the term "substantially." According to the Examiner's Answer, "[t]he term substantially in claims 2 and 10 is a relative term, which renders the claim indefinite." However, the fact that a claim contains a relative term does not, on its own, render the claim indefinite. As noted in Appellants' Appeal Brief, MPEP § 2173.05(b) states:

> The fact that claim language, including terms of degree, may not be precise, does not ***automatically*** render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. (Emphasis added.)

With regard to the term "substantially," the same section of the MPEP specifically states:

> The term "substantially" is often used in conjunction with another term to describe a particular characteristic of the claimed invention. It is a broad term. *In re Nehrenberg*, 280 F.2d 161, 126 USPQ 383 (CCPA 1960). The court held that the limitation "to substantially increase the efficiency of the compound as a copper extractant" was definite in view of the general guidelines contained in the specification. *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). The court held that the limitation "which produces substantially equal E and H plane

> illumination patterns" was definite because one of ordinary skill in the art would know what was meant by "substantially equal." *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988).

The Federal Circuit has specifically recognized that:

> The criticized words ["substantially"] are ubiquitous in patent claims. Such usages, when serving reasonably to describe the claimed subject matter to those of skill in the field of the invention, and to distinguish the claimed subject matter from the prior art, have been accepted in patent examination and upheld by the courts.

Andrew *Corp. v. Gabriel Electronics*, 847 F.2d 819, 821 (Fed. Cir. 1988).

Appellants maintain that the meaning of "substantially free of crystalline forms" as used in claims 2 and 10 is clear to one of skill in the art. According to the Examiner, "the specification does not provide a standard for ascertaining the requisite degree [of substantially free]." Such a finding is clearly in error, since the first full paragraph on page 7 of the specification states the term "substantially free of crystalline forms of cetirizine dihydrochloride," as used herein, means that the crystalline form of cetirizine dihydrochloride ***cannot be detected by methods known to those skilled in the art***." (Emphasis added.) Since the specification also teaches that "X-ray diffraction provides a convenient and practical means for quantitative determination of the relative amounts of crystalline and amorphous forms" (page 8), one of skill in the art is readily apprised of both the scope of the claims and their practice. No more can be demanded of Appellants. *See Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624 (Fed. Cir. 1985) ("If the claims, read in the light of the

specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more.").

Accordingly, Appellants maintain that the rejection of claims 2 and 10 for indefiniteness was made in error and should be reversed.

B. The Examiner maintains that claims 1-16 are anticipated by any of Tang, Pflum and Van de Venne, which disclose levocetirizine dihydrochloride without reference to its solid state form. According to the Examiner' Answer, the amorphous nature of the claimed levocetirizine dihydrochloride is merely an inherent property of the prior art material. The Examiner cites to MPEP § 2112 for the proposition that "Something which is old does not become patentable upon discovery of a new property." The Examiner also cites to *Ex parte Anderson*, 21 USPQ2d 1241, 1251 (Bd. Pat. App. & Inter. 1991) for the proposition that "there is ample precedent for shifting the burden to an applicant to reproduce a prior art product whose final structure or properties are, at least, in part determined by the precise process used in its manufacture."

The problem with the Examiner's inherency theory is two-fold. First, Appellants' amorphous levocitirizine dihydrochloride is not a new property of an old compound, but rather a ***new entity***. The Federal Circuit and the CCPA have consistently held new solid state forms to be patentable over other forms of the same compound, thereby fulfilling the novelty requirement. *See, e.g.*, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043 (Fed. Cir. 1995) (ranitidine form 2 novel over

form 1); *Bristol-Myers Co. v. U.S. Int'l Trade Comm'n*, 892 F.2d 1050, 1989 WL 147230 (Fed. Cir. Dec. 8, 1989) (unpublished decision) (Bouzard cefadroxil monohydrate novel and unobvious over other cefadroxil forms); *Silvestri v. Grant*, 496 F.2d 593 (CCPA 1974) (ampicillin B patentably distinct from ampicillin A); *In re Irani*, 427 F.2d 806 (CCPA 1970) (crystalline anhydrous ATMP novel and unobvious over amorphous ATMP); *In re Cofer*, 354 F.2d 664 (CCPA 1966) (crystalline 2,2-B novel and unobvious over liquid 2,2-B).

Similarly, numerous decisions from the Board of Patent Appeals and Interferences have also held new solid state forms to be patentable over other earlier described forms. *See, e.g.*, *See Ex parte Havens*, Appeal No. 2001-0091 for Application No. 08/732,254, now U.S. Patent No. 6,452,007 (BPAI 2003); *Ex parte Reguri*, Appeal No. 2007-0313 for Application No. 10/414,447, now abandoned (BPAI 2007); *Ex parte Zimmerman*, Appeal No. 2003-0919 for Application No. 09/463,097, now U.S. Patent No. 6,894,051 (BPAI 2003); *Ex parte Glover*, Appeal No. 2006-2861 for Application. No. 10/007,272, now U.S. Patent No. 7,297,683 (BPAI 2007); *Ex parte Polniaszek*, Appeal No. 2001-1805 for Application No. 08/732,254, now U.S. Patent No. 6,452,007 (BPAI 2003); *Ex parte Gala*, Appeal No. 2001-0987 for Application No. 09/169,109, now U.S. Patent No. 6,335,347 (BPAI 2002); *Ex parte Andrews*, Appeal No. 2002-0941 for Application No. 09/166,445, now U.S. Patent No. 6,713,481 (BPAI 2003); *Ex parte Portmann*, Appeal No. 2003-1199 for Application No. 09/125,329, now U.S. Patent No. 6,740,669 (BPAI 2004); *Ex parte Meisel*, Appeal No. 2002-0438 for Application No. 09/181,671, now U.S. Patent No. 6,538,151 (BPAI 2002); *Ex*

parte Li, Appeal No. 2007-1348 for Application No. 10/650,253, now U.S. Patent No. 7,282,486 (BPAI 2007); and *Ex parte Aronhime*, Appeal No. 2009-003073 for Application No. 11/171,579, now abandoned (BPAI 2009).

Second, the Examiner has not provided the requisite quantum of evidence to justify shifting the burden of proof to Appellants in this case. To establish inherency, "the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citations omitted); see also *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) ("In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the teachings of the applied prior art") (emphasis in original).

Here, the generalized passages pointed to in Tang, Pflum, and Van de Venne by the Examiner do not provide a basis in fact and/or technical reasoning that the allegedly inherent characteristic, in this case amorphous levocetirizine dihydrochloride, ***necessarily*** flows from the teachings of the applied prior art. Tang, Pflum, and Van de Venne at most disclose levocetirizine dihydrochloride, with no teaching or suggestion that it is in the amorphous state. Certainly there is no description in Tang, Pflum, or Van de Venne of Appellants' process for

preparing the solid amorphous levocetirizine dihydrochloride recited in claims 6-18. *See* page 12. As such, it is error for the Examiner to attempt to shift the burden to Appellants to reproduce the prior art levocetirizine dihydrochloride and demonstrate that it is not amorphous. Indeed, with regard to Van de Venne, it would be impossible for Appellants to do so since they do not describe how levocetirizine dihydrochloride was prepared.

Ex parte Anderson (Appeal No. 90-2106), 21 USPQ2d 1241, relied upon by the Examiner, is not to the contrary. In *Anderson*, claims directed to interpolymers of ethylene and alpha-olefins were rejected as anticipated by the work of Witt and Leatherman. The applicant admitted that Witt and Leatherman made copolymers of ethylene and pentene and hexane at a date earlier than that of the claimed invention, and that these copolymers had melt index, density, co-monomer weight percent, and crystallinity values within the ranges recited in the claims. The claims, however, recited tear strength values, which Witt and Leatherman did not measure. The applicant argued that it was improper for the examiner to place the burden on the applicant to establish that Witt and Leatherman copolymers did not inherently possess the recited tear strength values. The board disagreed, finding that the USPTO can require an applicant to prove that a prior art product lacks an inherent characteristic where there is identity or substantial identity between the products and the processes used in their manufacture. *See* pages 1251-53.

Here, in contrast the *Anderson* situation, the Examiner has not shown that: 1) the levocetirizine dihydrochloride in Tang, Pflum, or Van de Venne was

produced by a process similar enough in nature to that disclosed in the subject application; or 2) that the claimed levocetirizine dihydrochloride and the levocetirizine dihydrochloride in Tang, Pflum, or Van de Venne exhibits an identity or substantial identity of express characteristics at a sufficient level, to justify the conclusion that the any one of the prior art levocetirizine dihydrochlorides is amorphous. As such, the Examiner's inherency theory must fail. *See Reguri*, *supra* ("Thus, the evidence of record shows that that the prior art product was made by a different method and has different physical properties than the claimed Form[s]. The evidence does not support the Examiner's conclusion that it is reasonable to expect the prior art product to contain either of the claimed crystalline forms . . . . We therefore reverse the rejection under 35 U.S.C. § 102(b)."); *Ex parte Glover*, *supra* (same).

Accordingly, Appellants maintain that the rejection of claims 1-16 for anticipation was made in error and should be reversed.

C. The Examiner maintains that claims 17 and 18 are obvious over Van de Venne. According to the Examiner' Answer, although Van de Venne does not specifically disclose amorphous levocetirizine dihydrochloride, it would have been obvious to modify the teachings of Van de Venne to obtain the compositions claimed in the subject application. The Examiner cites a passage in Hancock, *Pharm Res.*, 2000 ("Hancock") as motivation: "Amorphous pharmaceuticals are markedly more soluble than their crystalline counterparts."

As discussed above, Van de Venne does not describe how levocetirizine dihydrochloride was prepared, and therefore would not have suggested amorphous levocetirizine dihydrochloride. As explained in Appellants' Appeal Brief, notwithstanding the fact that some morphous compounds might tend to be more soluble than their crystalline counterparts, it remains the case that the pharmaceutical industry still faces significant challenges in the identification and isolation of amorphous pharmaceutical compounds. Hancock themselves recognize this by stating on page 397 that "almost all workers cite significant experimental difficulties during solubility measurements due to crystallization of the amorphous drug." This is why Almarsson and Gardner ("Novel Approaches to Issues of Developability," *Current Drug Discovery,* January 2003, pp. 21-26, a copy of which is appended to Appellants' Appeal Brief) conclude that "In general, pharmaceutical companies make every effort to avoid committing to the development of an amorphous compound."

As such, one of ordinary skill in the art could not have predicted with any reasonable certainty whether the amorphous form of levocetirizine dihydrochloride could be isolated based on the generic teaching of Van de Venne without undue experimentation, even if a motivation to try existed. Such unpredictability precludes a finding of obviousness. *See Bristol-Myers*, *supra*, ("The law of § 103 requires quite a different inquiry from that conducted by the ALJ. The correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether

it would have been obvious to ***make the Bouzard monohydrate, based on the prior art***.") (emphasis added); *Polniaszek*, *supra* ("The prior art relied upon by the examiner does not teach this specific polymorph as claimed by the appellants. The Examiner failed to demonstrate that the prior art even recognized that the claimed compound exists in different polymorphic forms, or that there is a known or obvious way to manufacture the specific polymorphic form claimed").

Furthermore, the compositions recited in Appellants' claims 17 and 18 require specific moisture contents. Although the Examiner recognizes that Van de Venne is silent regarding moisture content, no evidence has been provided to suggest that such moisture contents would have been obvious. *See Ex parte Reddy*, Appeal No. 2008-4197 for Application No. 10/651,306, now U.S. Patent No. 7,612,098 (BPAI 2009) (no evidence in record whether "the prior art hydrous magnesium omeprazoles would be expected to have a moisture content of 2 percent to 10 percent."). The Examiner has simply ignored the claim limitations in arriving at the ultimate legal conclusion of obviousness. This clearly constitutes reversible error on the part of the Examiner. *See In re Glass*, 472 F.2d 1388, 1392 (CCPA 1973) ("It is error to ignore specific limitations distinguishing over the references.").

Accordingly, Appellants maintain that the rejection of claims 17 and 18 for obviousness was made in error and should be reversed.

CONCLUSION

For the foregoing reasons, Appellants maintain that each of the Examiner's rejections is improper, and reversal of the rejections is therefore appropriate and is respectfully solicited.

Date: July 2, 2010

Respectfully submitted,

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